EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 December 2009
EMA/841003/2009
Patient Health Protection

Fourth pandemic pharmacovigilance weekly update

This update has been prepared by the European Medicines Agency to provide a summary of the adverse drug reactions reported after use of centrally authorised pandemic vaccines and antivirals. It also provides information on the evolution of the H1N1 pandemic, an estimate of how many doses have been distributed or administered in Europe, and other available information on the benefits and risks of the vaccines and antivirals. The centrally authorised pandemic medicines concerned by this update are the vaccines Celvapan, Focetria and Pandemrix and the antiviral Tamiflu.

This update includes reports of *suspected* reactions that were observed after the medicines were administered. This does not mean that these reactions have been caused by the medicine. They could be a symptom of another illness or they could be associated with another product taken by the patient. Healthcare professionals are actively encouraged to report events following vaccination.

It should be noted that, due to differences in the numbers of persons having received each vaccine, the number of reports shown for the three different vaccines cannot be used for a comparison between them regarding safety or benefit-risk balance.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system managed by the European Medicines Agency for the collection and evaluation of reports of suspected adverse drug reactions to medicinal products. It allows the transfer of reports from national regulatory agencies and marketing authorisation holders to the European Medicines Agency, and the early detection and monitoring of possible safety signals in relation to reported adverse reactions. This update includes reports received in EudraVigilance up to 13 December 2009. The graphs represent aggregated data related to the European Economic Area (EEA) only, and provide an overview of the reporting situation in the EEA. The updated safety information also considers worldwide cases from EudraVigilance. A list of the most frequently reported suspected adverse reactions is also presented for the organ systems with the largest number of reports. A single patient may experience several reactions that will be included in a single report. Therefore the number of reactions may not be equal to the number of patients.

The weekly update may also include information on the safety of vaccines made available by Member States.

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Key message

At least 28 million persons including at least 218,000 pregnant women have been vaccinated to-date in Europe with one of the three centrally-authorised vaccines. The most frequent adverse reactions that have been reported are non serious and as expected.

The benefit-risk balance of the pandemic vaccines and antivirals used for the current H1N1 influenza pandemic continues to be positive.

On 18 December 2009, the European Medicines Agency published a press release informing the public that immunogenicity data submitted for Focetria and Pandemrix confirm the currently approved dosing schedule, namely a single dose of these vaccines is able to trigger an immune response that may be sufficient in some age groups to give protection against the H1N1 pandemic influenza.

Up to 13 December 2009, 13 cases of Guillain-Barré syndrome (GBS) and 1 case of Miller-Fischer syndrome (a variant of GBS) have been reported in relation with Celvapan, Focetria or Pandemrix. Given that more than 28 million persons have been vaccinated, 14 reported cases does not exceed the number of cases expected to naturally occur in the vaccinated population.

For further information on the established adverse reactions included in the authorised product information for centrally authorised pandemic vaccines (Celvapan, Focetria, Pandemrix) and antivirals (Tamiflu), visit the Agency's Pandemic influenza (H1N1) website.

For information regarding products authorised at a national level, please contact the relevant National Competent Authority (see Regulatory bodies in the European Union for links).

Pandemic information

According to the European Centre for Disease prevention and Control (ECDC) (for latest report click here), a total of 1,652 fatal cases of A/H1N1 influenza in the EU and European Free Trade Association (EFTA) countries have been reported as of 21 December 2009. While most deaths have to date been in Western Europe there are increasing numbers of deaths being reported from Central and Eastern Europe. However, because of lack of laboratory confirmation and underreporting, among other factors, this is likely to be a gross underestimation of the true number of fatalities associated with the pandemic.

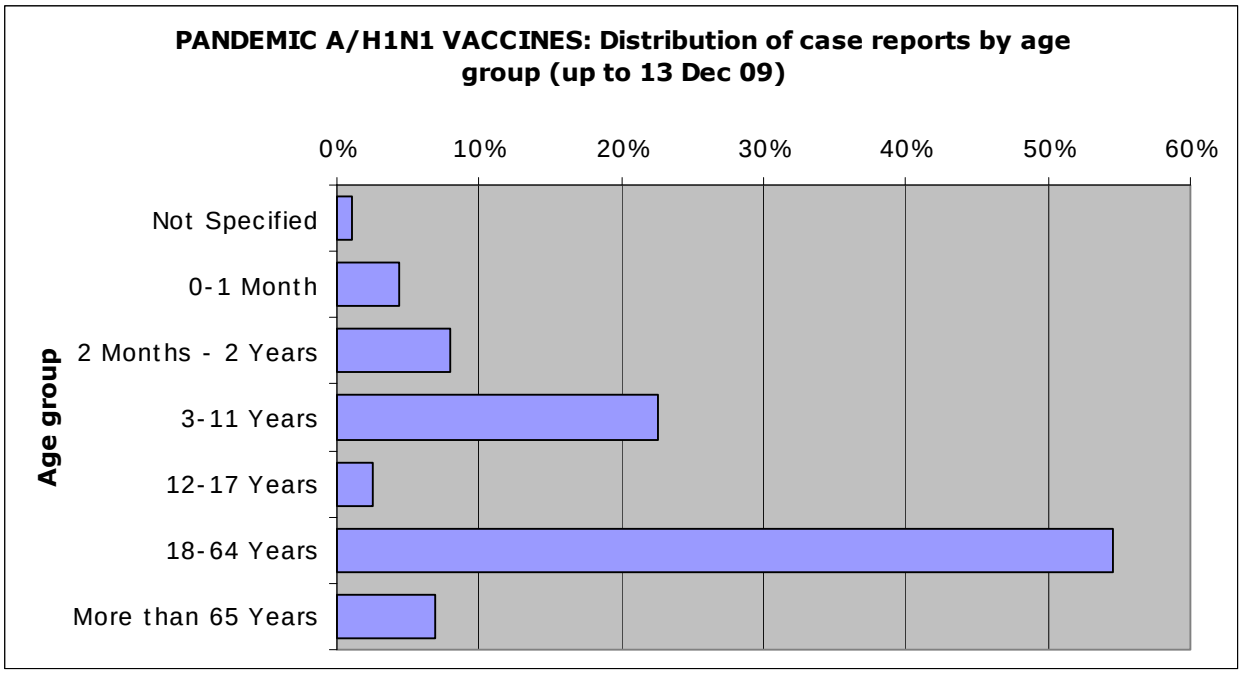
In its Weekly influenza surveillance overview of 18 December 2009, the ECDC concludes that most countries are witnessing medium influenza intensity with only five reporting high to very high levels. In the majority of countries, activity is still widespread. Nineteen countries reported decreasing rates of influenza-like illness or acute respiratory infection for at least the last two weeks. While the proportion of influenza-positive sentinel samples continued to decline, the 2009 pandemic influenza A(H1N1) virus still accounted for 99% of all sub-typed viruses in sentinel patients and for 97% in patients with severe acute respiratory infection. Approximately one third of these patients were known to have required admission into an intensive care unit.

See also the ECDC website for more information on the ECDC.

In its Weekly Update dated 18 December, the World Health Organisation states that, as of 13 December 2009, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 10,582 deaths.

Overview of centrally authorised vaccines

As of 13 December 2009, a total of 8,745 reports had been received by EudraVigilance since the authorisation of the three centrally-authorised vaccines. This represents an increase of 2,644 reports compared with the previous update. It reflects the increase in the number of vaccinated people. The graph below displays the age distribution of patients having experienced an adverse reaction reported to Eudravigilance. From available information on the age distribution of vaccinated people in a limited number of Member States, the percentages shown in the graph seem to reflect the age distribution of the vaccinations, except in the 0-1 month age group where are counted reports of pregnancy outcomes.



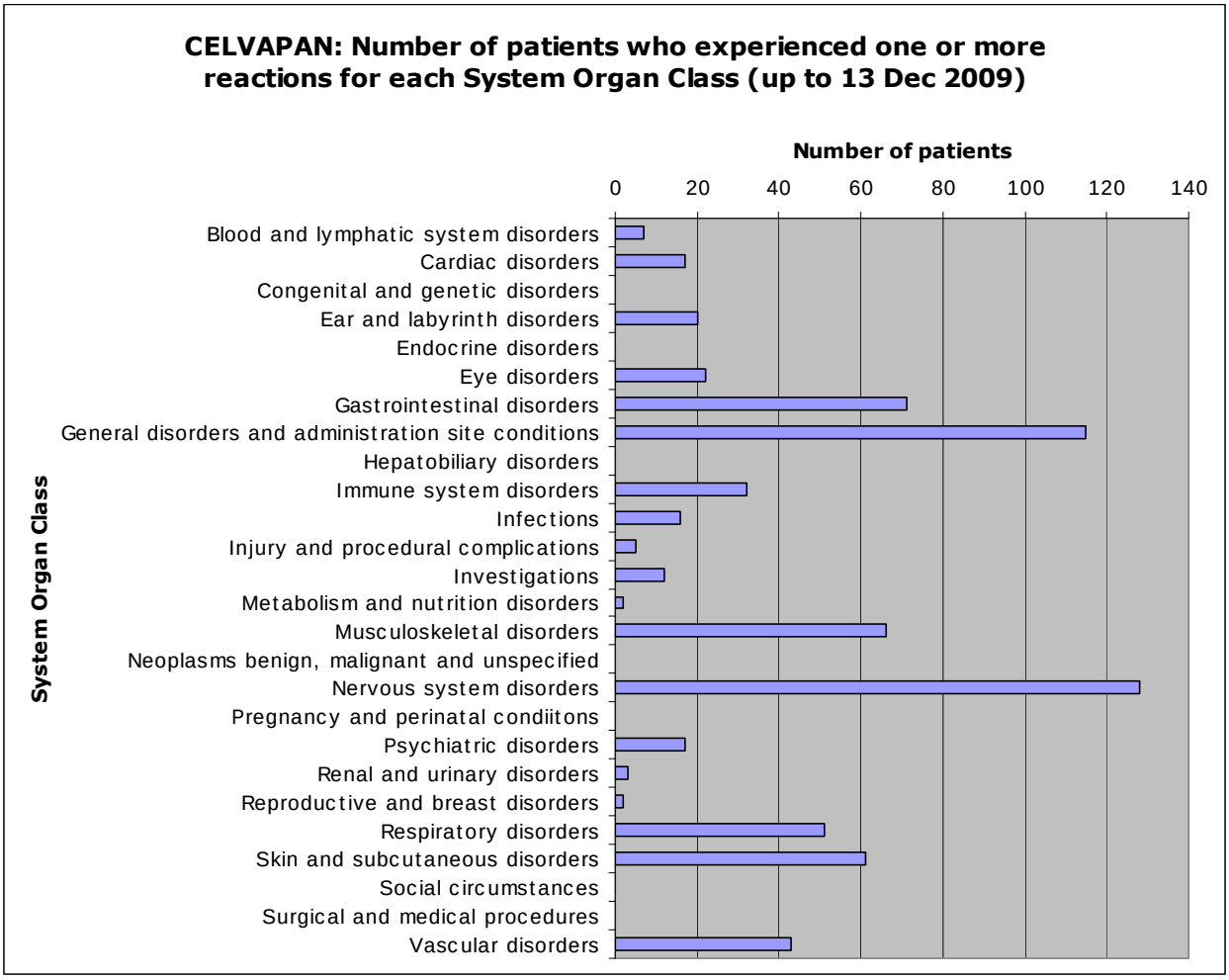
Data available on 22 December 2009 from Member States and from the companies indicate that at least 74.6 million doses have been distributed and at least 28.7 million patients have been vaccinated in the EEA with one of the three centrally-authorised vaccines. From limited information received from 7 countries by 22 December 2009, at least 218,000 pregnant women have been vaccinated.

A review of cases of polyneuropathies reported up to 13 December for the three vaccines identified 13 cases of Guillain-Barré syndrome (GBS) and 1 case of Miller-Fischer syndrome (a variant of GBS). In four cases, there has been no confirmation of the diagnosis. Patients were aged 24 to 79 years old and the reported delay of onset ranged from 1 to 31 days. Several factors are known to play a role in the occurrence of GBS, such as a viral infection, a *Campylobacter jejuni* enteritis, a previous surgical procedure, lymphoma or lupus erythematosus. Taking into account the more than 28 million patients vaccinated with one of the three vaccines and an overall background incidence rate of 2 cases per 100,000 persons and per year, the 14 cases reported in relation to the pandemic vaccines is lower than the number of cases that is expected to occur naturally in the vaccinated population. However, every new case will be closely followed.

Celvapan

As of 13 December 2009, a total of 251 reports had been received in EudraVigilance (increase of 35 reports since the previous update). According to company information, a total of 3,399,200 doses had

been distributed to EU Member States up to 16 November 2009[1]. Based on Member States' information (and corrected information received from one Member State since the last update), it is estimated that at least 255,000 patients have been vaccinated with Celvapan in the EEA.



Distribution of adverse reactions by System Organ Class

- In reports received from the EEA, the most frequent suspected adverse reactions experienced by patients in each System Organ Class since the authorisation of the vaccine are:
  - Nervous system disorders: headache, dizziness, paraesthesia, syncope;
  - General disorders and administration site conditions: pyrexia, chills, malaise, fatigue, asthenia;
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain
  - Musculoskeletal disorders: arthralgia, myalgia, pain in extremity;
  - Skin and subcutaneous conditions: pruritus, rash, urticaria, erythema;
  - Respiratory disorders: dyspnoea, oropharyngeal pain, cough;
  - Vascular disorders: pallor, hypotension, flushing;
  - Immune disorders: hypersensitivity, anaphylactic reaction.

[1] As stated by the marketing authorisation holder in the simplified Periodic Safety Update Report (S-PSUR) received 30 November 2009.

- Since authorisation, 2 fatal cases have been reported from the EEA in relation with Celvapan. These cases have been described in previous weekly updates.

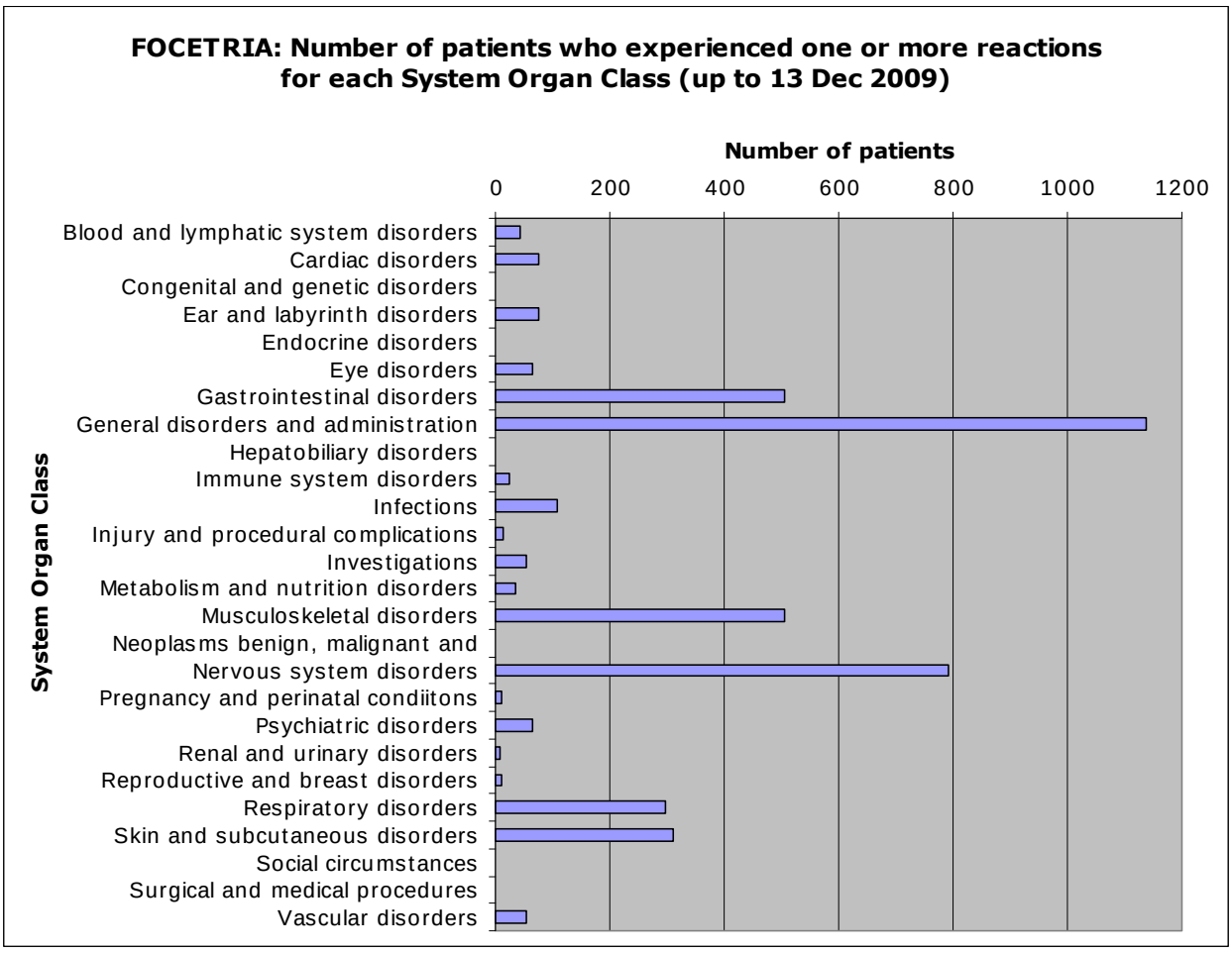
Updated safety information

- The most frequently suspected adverse reactions reported in children since authorisation include hypersensitivity, dizziness, headache, vomiting, syncope, vision blurred, nausea, and pallor.
- Since authorisation, 21 distinct cases of eye disorders reported as serious have been received. The most frequent suspected reaction has been blurred vision. Other reported reactions have included eye swelling and pain and single cases of conjunctivitis, eye rolling, eye stinging, mydriasis, photophobia and visual impairment. About one third of the patients had a medical history of asthma or allergies. According to the product information, conjunctivitis is an adverse reaction that has been observed with the Celvapan vaccine containing the H5N1 vaccine strain. Eye disorders will be further monitored in relation to the H1N1 vaccine.

Focetria

As of 13 December 2009, a total 2,239 reports had been received in EudraVigilance (increase of 517 reports since the previous update). Data available on 22 December 2009 from Member States and from the company[2] indicate that at least 27.4 million doses of Focetria had been distributed in the EEA, and at least 7.4 million individuals had been vaccinated.

[2] As stated by the marketing authorisation holder in the simplified Periodic Safety Update Report (S-PSUR) dated 8 December (data lock point: 30 November 2009).



Distribution of adverse reactions by System Organ Class

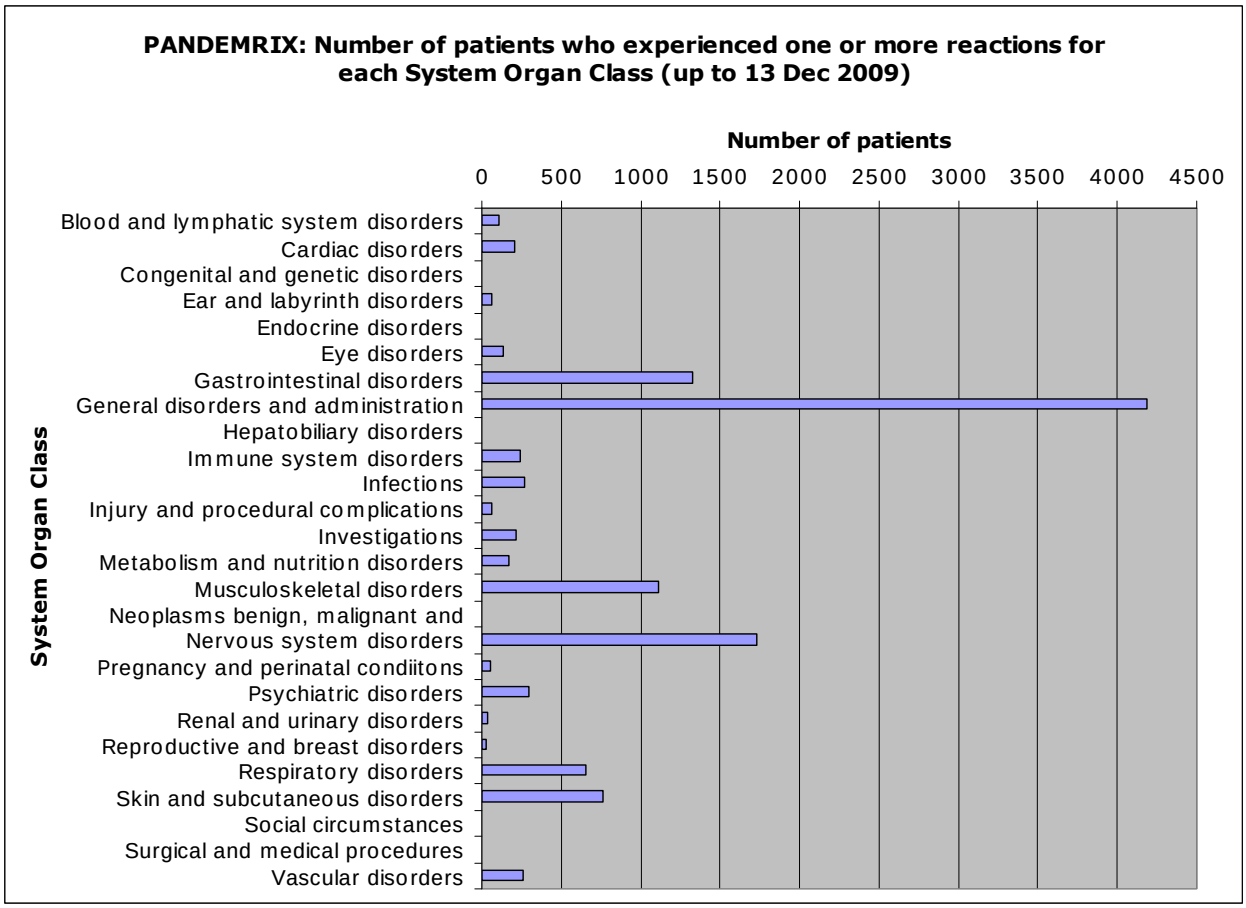
- In reports received from the EEA, the most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:
  - General disorders and administration site conditions: pyrexia, fatigue, injection site pain, influenza-like illness, malaise, chills, injection site erythema, injection site swelling;
  - Nervous system disorders: headache, dizziness, paraesthesia, dysgeusia, somnolence, syncope, tremor;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, neck pain, muscular weakness, muscle spasms;
  - Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain;
  - Skin and subcutaneous conditions: rash, pruritus, erythema, urticaria, hyperhydrosis, rash pruritic, dermatitis allergic;
  - Respiratory disorders: cough, dyspnoea, oropharyngeal pain;
  - Infections: rhinitis, nasopharyngitis.
- Since the last update, 3 cases with a fatal outcome have been received from the EEA. They concerned two patients aged 89 and 62 years old with a pre-existing cardiac disorder and a 87 year-old patient whose death was considered unlikely to be related to the vaccine by the reporter.

Updated safety information

- The most frequently suspected adverse reactions reported in children since authorisation include pyrexia, injection site pain, headache, vomiting, hyperpyrexia, cough, nausea, myalgia, influenza-like illness, rash, fatigue and dyspnoea.
- Since authorisation, 6 cases of facial palsy were reported in relation to the administration of Focetria. Facial palsy is a paralysis of a cranial nerve that supplies all the muscles concerned with facial expression, and it often affects only one side of the face. These cases were all female patients, aged 23 to 58 years old. The time to onset after vaccination was highly variable, ranging from 1 hour to 11 days. There are many possible causes for the occurrence of facial palsy, but in most cases the cause is unknown. Data from the United-Kingdom have shown that the incidence rate of this disorder can been estimated to be 29 per 100,000 persons and per year in the age group 18 to 44 years old and 36 per 100,000 in the age group 45 to 65. Available data also show that the age group 18-64 may represent about 55% of the vaccinated population. Based on a number of at least 7.4 million vaccinated patients with Focetria, it can be estimated that at least 35 cases would have been expected to occur naturally in the vaccinated population within 11 days after the vaccination. There is therefore no indication that the vaccine could increase the risk of facial palsy within that time frame.
- Since authorisation, 6 cases of intra-uterine death have been reported to Eudravigilance in relation to Focetria. Two cases do not mention the gestational age, and it is therefore not known if the event could be a spontaneous abortion or a perinatal death. For the other cases, the gestational age ranged from 30 to 38 weeks and the event occurred from 2 to 8 days after vaccination with Focetria. Given that foetal death generally occurs at a frequency of 4 to 5 per 1,000 deliveries and that at least 84,000 pregnant women have been vaccinated with Focetria, the data do not suggest that the vaccine could increase the risk of foetal death.

Pandemrix

As of 13 December 2009, a total of 6,255 reports had been received in EudraVigilance (increase of 2,092 reports since the previous update). Data available on 22 December 2009 from Member States and from the company indicate that at least 44.9 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 21.1 million individuals have been vaccinated.



Distribution of adverse reactions by System Organ Class

- In reports received from the EEA, the most frequent suspected adverse reactions experienced by patients in each SOC since the authorisation of the vaccine are:
  - General disorders and administration site conditions: pyrexia, hyperpyrexia, injection site pain, fatigue, influenza-like illness, malaise, chills, oedema peripheral, injection site swelling, pain;
  - Nervous system disorders: headache, dizziness, paraesthesia, somnolence, syncope, hypoaesthesia, crying, lethargy, convulsions, tremor;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, paraesthesia oral, dry mouth, swollen tongue, lip swelling, abdominal discomfort;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness;
  - Skin and subcutaneous conditions: rash, erythema, hyperhydrosis, urticaria, pruritus, rash generalised, angioedema, cold sweat, swelling face, rash erythematous;
  - Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, pharyngeal oedema, throat tightness;
  - Vascular disorders: pallor, circulatory collapse, flushing, hypotension, hypertension, hot flush, peripheral coldness;
  - Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, nightmare.

  - Infections: rhinitis, nasopharyngitis, herpes zoster, influenza, pneumonia;
  - Immune disorders: anaphylactic reaction, hypersensitivity, anaphylactic shock;
- Since the last update, 24 cases with a fatal outcome have been received from the EEA. In the majority of the cases, the cause of death was linked to an underlying cardiac or pulmonary disease. Fatal cases included two children aged 2- and 1-year old who had a pre-existing cardiomyopathy and pulmonary disease, respectively. In 5 cases of unexplained sudden death, additional information has been requested.

Updated safety information

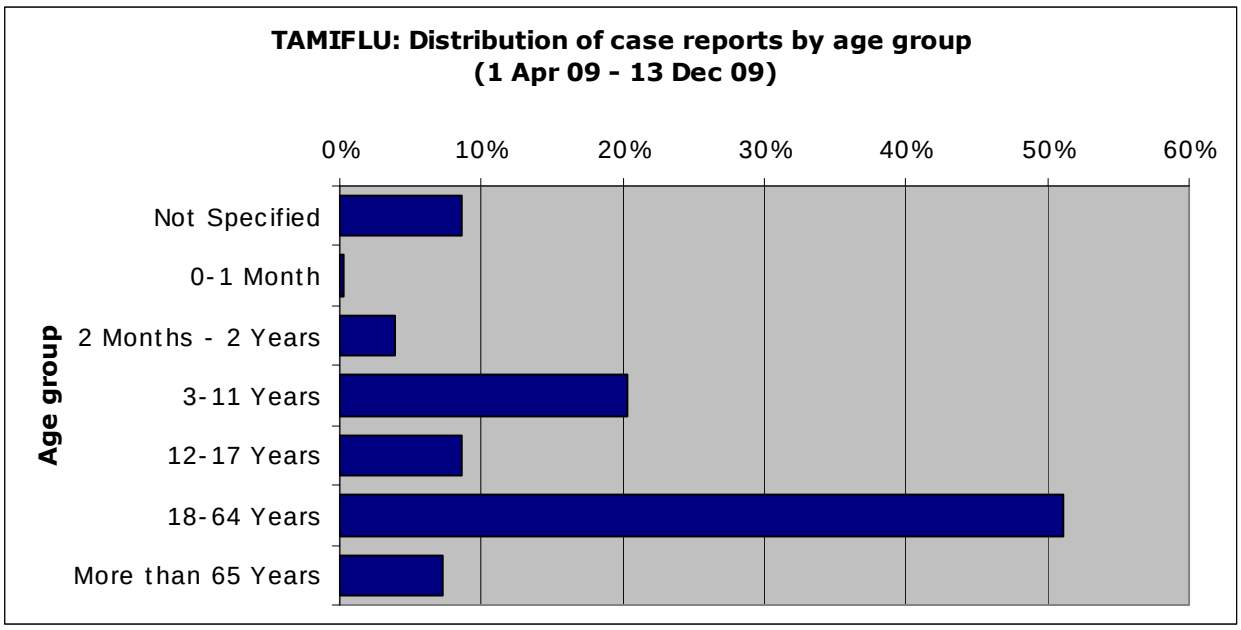
- The most frequently suspected adverse reactions reported in children since authorisation are pyrexia, hyperpyrexia, vomiting, injection site pain, headache, diarrhoea, cough, fatigue, abdominal pain, decreased appetite, rash, malaise, nausea, influenza-like illness, listless, myalgia and somnolence.
- Since authorisation, 3 cases of idiopathic thrombocytopenic purpura (ITP) and 1 case of autoimmune thrombocytopenia have been received in association with Pandemrix. One case of ITP occurred on the same day as the vaccination, the second case occurred the day following the vaccination and the third case occurred more than one month later. In the three cases of ITP, the patient already had a medical history of ITP. The report of autoimmune thrombocytopenia contains limited information. One case of idiopathic thrombocytopenia was also received in relation to an unbranded vaccine which is probably Pandemrix. The patient had suffered from viral infection which was confirmed to be H1N1 influenza virus. In these five cases, there is no indication that the vaccine could have caused the event. Taking into account the number of persons vaccinated with Pandemrix in Europe, this number of 5 observed cases is lower that the number of cases of ITP or autoimmune thrombocytopenia that would be expected to occur in the population, estimated to be between 5 and 10 per 100.000 persons aged 45 years old or more and per year.
- Since authorisation there have been 5 cases of sudden hearing loss reported in patients who had received Pandemrix. Patients were aged from 25 to 82 years old. The time to onset ranged from a few hours to 7 days after vaccination. Of the 5 cases, 3 are poorly documented and do not allow to evaluate the relationship with the vaccine. Hearing tests were only reported in one case describing an 82-year-old female for whom a cerebral haemorrhage was finally suspected. There are many possible causes to sudden hearing loss, and some cases inevitably occur in temporal association with the vaccination, but this does not mean they have been caused by the vaccine. This issue will nevertheless be closely monitored.
- Three reports of seizures with a fatal outcome in known epileptic patients have been reported in temporal association with the Pandemrix vaccine. In one case the patient had not experienced a seizure for 21 years. In the two other cases, the patient had a poor epilepsy control. A search for additional cases across Europe revealed a further 34 cases of seizures occurring in known epileptic patients following Pandemrix. Given that a very large number of persons have received Pandemrix, no conclusion about a causal relationship with Pandemrix can be drawn at this stage, but this issue is being further investigated.
- One report of confirmed delayed hypersensitivity reaction has been received. This report concerns a woman who experienced, 2 days after vaccination with Pandemrix, a maculopapular erythema and a small haematoma at the injection site. Three days after vaccination, she experienced redness on the chest, itching and an inflammatory reaction. The diagnosis showed a delayed

hypersensitivity reaction of type IV. The events improved. Cases of delayed hypersensitivity will be closely monitored.

Antiviral medicines

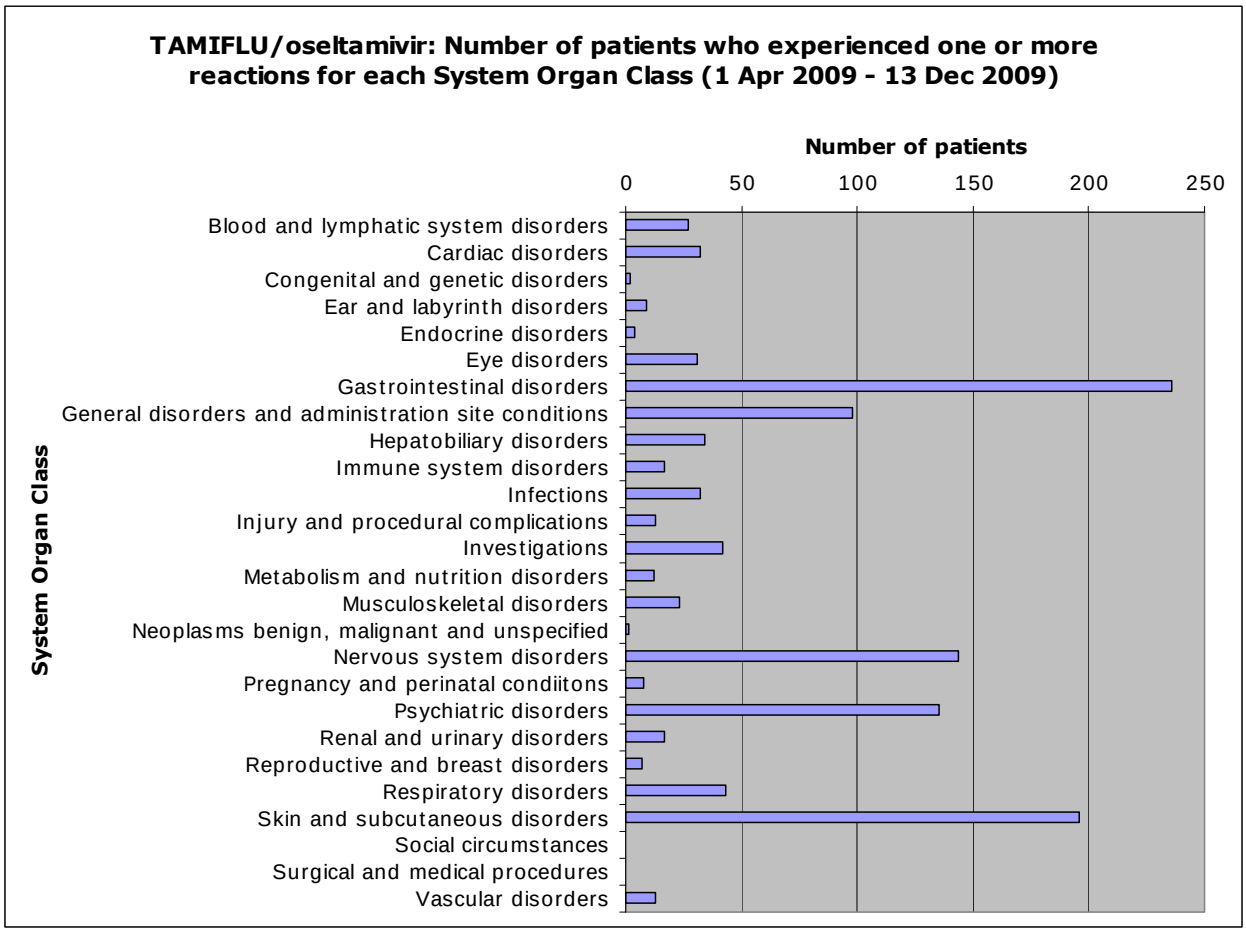
Tamiflu

From 1 April to 13 December 2009, a total number of 807 reports worldwide have been received in EudraVigilance (increase of 54 reports since the previous update). The graph below displays the age distribution of patients having experienced an adverse reaction reported to Eudravigilance.



According to information received from the marketing authorisation holder dated 26 November 2009, the patient exposure to oseltamivir is estimated to be approximately 4.3 million patients during the period 1 October 2009 to 31 October 2009 and 13.0 million patients during the period from 1 May 2009 to 31 October 2009[3].

[3] As stated by the marketing authorisation holder in the Pandemic Safety Report dated 26 November 2009.



Distribution of adverse reactions by System Organ Class

- The adverse reaction reports received from the EEA are consistent with the safety profile described in the product information. The most frequent reported suspected adverse reactions experienced by patients in each SOC:
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, mouth ulceration, lip swelling;
  - Skin and subcutaneous conditions: rash, rash generalised, urticaria, swelling face, Stevens-Johnson syndrome, pruritis, rash pruritic;
  - Nervous system disorders: headache, convulsion, paraesthesia, dizziness, tremor, cardiovascular accident;
  - Psychiatric disorders: hallucination, confusional state, nightmare, insomnia, anxiety, delirium, hallucination, visual;
  - General disorders and administration site conditions: malaise, oedema peripheral, fatigue, chest pain, drug interaction, influenza-like illness;
  - Respiratory disorders: epistaxis, dyspnoea.
- Since the last update, 2 fatal cases have been received from the EEA. For these fatal cases, a causal association with Tamiflu treatment has not been established. It should be noted that healthcare professionals are actively encouraged to report events following administration of

medicinal products and coincidental events (e.g. due to underlying medical conditions) that could have occurred anyway, in the absence of therapy.